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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/764,328	01/23/2004	Charles D. Boyd	PXE-001C1	6535

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EXAMINER	
WILDER, CYNTHIA B	
ART UNIT	**PAPER NUMBER**
1637	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/29/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/764,328	BOYD ET AL.	
	Examiner	Art Unit	
	Cynthia B. Wilder, Ph.D.	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-78* is/are pending in the application.

4a) Of the above claim(s) *65,66 and 74-78* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-64 and 67-73* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *8/05 & 12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant election without traverse of the mutation at codon 1141 and the species election of the nucleic acid sequencing assay filed on November 9, 2006 is acknowledged. Claims 1-33 have been deleted. Claims 34-78 are pending. Claims, 65, 66, 74-78 are withdrawn from consideration. Claims 34-64, 67-73 are discussed in this Office Action.

Specification

2. The disclosure is objected to because of the following informalities:

(a) The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code at page 13, line 13; page 45, line 2 and page 52, line 6. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. For example, by deleting "http://". See MPEP § 608.01.

(b) The use of the trademark "The Sequencher" at page 45, line 10 has been noted in this application. It should be *capitalized* wherever it appears and be accompanied by the generic terminology.

Although the use of trademarks is permissible in patent applications, the proprietary nature of the marks should be respected and every effort made to prevent their use in any manner which might adversely affect their validity as trademarks.

Claim Rejection 35 U.S.C. 112: Lack of Adequate Written Description

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 34-38, 41-63, 67-72 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The claims are broadly drawn to a method of detecting any PXE mutation in a patient, a method of identifying a patient at risk having children with PXE and a method for diagnosing PXE in a patient by detecting any mutation in an MRP6 nucleic acid or any pair of two MRP6 alleles.

The claims encompass a large genus of nucleic acid species of the MRP6 nucleic acid a large genus of mutations and/or alleles that may or may not be associated with PXE. The specification teaches the sequence of the MRP6 gene, which spans 31 exons (SEQ ID NO: 1) and identifies several unrelated PXE mutations in different exons of the MRP6 gene. The specification suggests that the MRP6 gene is associated to PXE mutations and thereby postulates that mutations in the MPR6 gene or the presence of any pair of two alleles may be correlated with detection of PXE. However, the specification does not provide any evidence of an association between the MPR6 nucleic acid and any mutation of PXE. The specification does not provide a limiting definition of what is encompassed by a "mutation" associated with PXE. In fact, the specification broadly disclose that "PXE associated mutations include mutations that affect the level of MRP6 protein expression in addition to mutations that alter the functional properties of an expressed MRP6 protein (page 13, line 30 to page 14, line 1). This description encompasses any possible mutation, which affects the level of MRP6 protein expression, or any possible mutation that alters the functional properties of an expressed MRP6 protein. That is, any single nucleotide or amino acid change in the MRP6 nucleic acid or protein could affect the

level of MRP6 protein expression or alter the functional properties of an expressed MRP6 protein, including silent mutations. While MPR6 nucleic acids comprising a mutation at an isolated position or a pair of two alleles of MPR6 at isolated positions, such as e.g., codon 1141 or codon 1141 & 1138 alleles, and/or methods that detects said mutation meet the written requirement of 35 U.S.C. 112, first paragraph, the specification does not disclose and fully characterize the genus of interrogating an MRP6 nucleic acid for the presence of any PXE mutation. *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states, "Applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed".

Therefore, given the large MRP6 gene sequence, the skilled artisan would not envision all of the contemplated mutations encompassed by the claimed genus. Thus, Applicants have not provided sufficient evidence that they were in possession, at the time of filing, of the claimed invention as broadly written.

Claim Rejection 35 U.S.C. 112: Enablement Rejection

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 34-63, 67-72 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for screening for the presence of a PXE mutation comprising, interrogating an MRP6 nucleic acid in patient sample for the presence of a

mutation, wherein the mutation is a mutation at codon 1141, it does not reasonably provide enablement for a method for detecting any PXE mutation in a patient comprising, interrogating an MRP6 nucleic acid in a patient ample for the presence of any mutation or any PXE mutation. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The first paragraph of section 112 requires the specification describe how to make and use the invention. There are many factors to be considered when determining whether there is sufficient evidence to support determination that a disclosure does not satisfy the enablement requirements and whether any necessary experimentation is "undue". These factors include but are not limited to: (1) quantity of experimentation necessary, (2) the amount of direction or guidance presented in the specification, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability of the unpredictability of the art and (8) the breadth of the claims. (See *In re Wands*, 858 F. 2d 731, 8 USPQ2d 1400, 1404, (Fed. Cir. 1988)) *(MPEP 2164.01(a))*.

The claims of the instant invention are broadly drawn to a method for detecting any PXE mutation in a patient by establishing if any mutation in an MRP6 gene is associated with PXE; a method for identifying a patient at risk of having children with PXE comprising interrogating an MRP6 nucleic acid in a patient sample for the presence of any MRP6 allele; a method for identifying a patient at risk of developing a PXE associated symptom comprising interrogating an MRP6 nucleic acid in a patient sample for the presence of any MRP6 allele and a method for

diagnosing PXE in a patient comprising interrogating an MRP6 nucleic acid in a patient sample for the presence of any pair of two MRP6 alleles.

The specification teaches the sequence of the MRP6 gene, which spans 31 exons (SEQ ID NO: 1) and identifies several unrelated PXE mutations at for example e.g., base 3775 and codon 1141 (see Tables 1 and 2). These mutations are located in different exons of the MRP6 gene. The specification suggests that the MRP6 gene is associated to PXE mutations and thereby postulates that mutations in the MPR6 gene or the presence of any pair of two alleles may be correlated with detection of PXE. However, the specification does not provide any evidence of an association between the MPR6 nucleic acid and any mutation of PXE. Case law has established that "To be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation'". *In re Wright* 990 F.2d 1557, 1561. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) it was determined that "[t]he scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art". The amount of guidance needed to enable the invention is related to the amount of knowledge in the art as well as the predictability in the art. Furthermore, the *Court in Genetech Inc. v. Novo Nordisk* 42 USPQ2d 1001 held that "[I}t is the specification, not the knowledge of one skilled in the art that must supply the novel aspects of the invention in order to constitute adequate enablement".

In the instant case, the claims are not commensurate in scope with the enabling disclosure because the claims are inclusive of methods for detecting a PXE mutation' method of identifying a patient's risk of having children with PXE and a method of diagnosing PXE in a patient in a

patient by detecting the presence of any mutation or allele or pair of two alleles in an MRP6 nucleic acid. The specification, at best, teaches several unrelated members of the broadly claimed genus of MRP6 nucleic acids comprising PXE mutations that have been identified by their complete structure, i.e., codon 1141. The broadest reasonable interpretation of the claims indicates that the claims are inclusive to a large genus of mutations or alleles present at any position on the MRP6 gene, including the promoter, 3' and 5' untranslated regions, exon and intron regions of the MRP6 gene. It is noted that the dependent claims 43-48 recited therein limit the mutations to non-conserved amino acid substitution, splice site in an intron, the promoter region, a polyA site, in an exon or exons 1-31 of the MRP6 gene. However, the specification does not teach any mutations that are non-conserved amino acid substitutions, mutations that are located in splice sites of introns, mutations that are located in the promoter region of the MRP6 gene, mutations that are located in the polyA region of the MRP6 gene, nor does the specification exemplify mutations that are located in exons 1-23, 25, 26 and 29-31. The specification only teaches for examples some mutations is exons 8, 12, 13, 16, 18, 23-30 as shown in Table 1 and *exemplify* by example three mutations in exon 24 (codon 1114, 1138 and 1141), one mutation in exon 27 (base 3775), and five mutations in exon 28 (1298, 1302, 1303, 1314, 1321) of the MRP6 gene as being associated with PXE (see page 46-47 and Fig 2 which clearly show an association of mutations at codon, 1114, 1138, 1141, 1259, 1298, 1302, 1303, 1314, 1321 and base 3775 being associated with PXE). While one could contemplate a nucleotide substitution at each and every position in the MRP6 gene, such substitutions are not considered to equivalent to PXE mutations. Rather, mutations in the MRP6 gene associated with PXE mutations represents a distinct group of nucleotide variations which are expected to occur at

only specific locations within the gene and consist of specific nucleotide alterations. In order for one of ordinary skill in the art to make and use this distinct group of nucleotide variations, one would have to test hundreds, if not thousands, of possible nucleotide alterations throughout the MRP6 gene that are PXE mutations. Thus, undue experimentation is deemed necessary to practice the instant invention commensurate fully in scope.

As to the level of unpredictability in the art concerning the instant invention, the specification teaches that one of these mutations, R1141X, which is the mutation at codon 1141, is "far more likely to be found in the general population than private mutations". (PG. 51, line 21-22), and "that two single-allele mutations (R1141X, R1339C) were found in control panels of normal individuals indicating that that heterozygote mutant (MRP6) ABCC6 alleles can be found in the normal population" (page 9, lines 20-23). These passages support the unpredictability regarding "mutations or alleles" shown be associates with PXE and their uses for diagnosis or identification of PXE. These passages further suggest that it is highly unpredictable that determining any mutation in MRP6 can be considered a mutation shown to be associates with PXE.

Therefore, in view of the high level of unpredictability in the art and in view of the lack of disclosure regarding the plethora of possible PXE mutations, undue experimentation would be required to practice the invention as broadly written.

Double Patenting

7. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection

is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

8. Claims 34-64 and 67-73 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6780587 B2.

An obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but an examined application claim is not patentably distinct from the reference claim(s) because the examined claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F. 2d 887, 225 USPQ 645 (fed. Cir. 1985). Although the conflicting claims are not identical, they are not patentably distinct from each other because both the claims of the instant invention and the claims 1-10 of US Patent 6,780,587 are drawn to a method for screening a patient for the presence of a PXE mutation. The claims of US Patent 6,780,587 only differs from the claims 34-64 and 67-73 in that the claim of US Patent '587 identifies wherein the mutation is selected from the group consisting of a mutation at codon, 1114, 1138, 1141, 1259, 1298, 1302, 1303, 1314 and 1321, whereas the claims of the instant invention either broadly encompasses any PXE

mutation The claims only differ in that the claims 34-63, 67-72 of the instant invention are broader in scope and encompasses any PXE mutation and the claims 64 and 73 are limited to a mutation at codon 1141.

Thus, the claims 34-64 and 67-73 of the instant invention falls entirely within the scope of the claims 1-10 of US patent 6,780,587. As the court stated in *In re Goodman*, 29 USPQ2d 2010 (CAFC 1993), "a second application-- "containing a broader claim, more generical in its character than the specific claim in the prior patent"--typically cannot support an independent valid patent. Miller, 151, U.S. at 198; See Stanley, 214 F.2d at 153. Thus, the generic invention, as noted above is "anticipated" by the species of the patented invention. Cf., Titanium metal corp. v. Banner, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985) (holding that an earlier species disclosure in the prior art defeats any generic claims). This court's predecessor has held that, without a terminal disclaimer, the species claims preclude issuance of the generical application. "*In re Van Ornum*, 686 F.2d 937, 944, 214 USPQ 761, 767 (CCPA 1982); *Schneller*, 397 F.2d at 354".

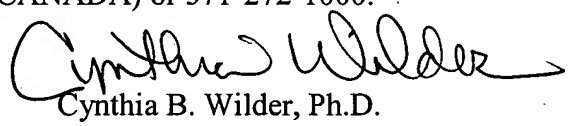
Conclusion

9. No claims are allowed. However, the claims have not been rejected under prior art because no prior art was found associating mutations of the MRP6 gene to PXE. The earliest teaching of PXE and MRP6 appears in the spring of 2000, which is after the filing date of the instant application.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cynthia B. Wilder, Ph.D. whose telephone number is (571) 272-0791. The examiner can normally be reached on a flexible schedule.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on (571) 272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.



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Art Unit 1637

1/18/2007